That which is claimed is:

1. A method of three-dimensional structure prediction and/or determination of a protein of interest of unknown structure, said method comprising:

comparing calculated rates of amide hydrogen exchange determined for a set of predicted possible structures for said protein of interest with experimental hydrogen exchange analysis of said protein of interest, and identifying one or more structures from said set of predicted possible structures having a calculated exchange rate profile closely matching the experimental exchange rate profile.

2. A method according to claim 1, wherein the quantity of the protein of interest used for said experimental hydrogen exchange analysis is less than about 10 micrograms.

3. A method according to claim 1, wherein said experimental hydrogen exchange analysis comprises determining the quantity of isotopic hydrogen and/or the rate of hydrogen exchange of a plurality of peptide amide hydrogens with said isotope.

4. A method according to claim 3, wherein said determining comprises generating a population of sequence-overlapping endopeptidase fragments of a protein labeled with a hydrogen isotope other than ^{1}H under conditions of slowed hydrogen exchange, and then deconvoluting fragmentation data acquired from said population of sequence-overlapping endopeptidase-generated fragments.

5. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated by cleaving said protein with an endopeptidase selected from the group consisting of a serine endopeptidase, a cysteine endopeptidase, an aspartic endopeptidase, a metalloendopeptidase, a threonine endopeptidase, and combinations of any two or more thereof.

6. A method according to claim 5, wherein said at least one endopeptidase is coupled to a support material.

7. A method according to claim 5, wherein said at least one endopeptidase is pepsin.

8. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated by two or more endopeptidases used in combination.

9. A method according to claim 4, wherein said at least one endopeptidase is newlase or Aspergillus protease XIII.

10. A method according to claim 4, wherein said at least one endopeptidase is an acid-tolerant Aspergillus protease.

11. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated at a pH of about 1.8 - 3.4.

12. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated at a pH of about 2 - 3.

13. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated at a pH of about 2.0 - 2.5.

14. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated at a pH of about 2.5 - 3.0.

15. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated in less than about five minutes of exposure to protease.

16. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated in less than about one minute of exposure to protease.

17. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments is generated in less than about 40 seconds of exposure to protease.

18. A method according to claim 4, wherein deconvoluting comprises:

comparing the quantity of isotope and/or rate of exchange of hydrogen at a peptide amide hydrogen with said isotope on a plurality of endopeptidase fragments in said population of sequence-overlapping endopeptidase-generated fragments with the quantity of isotope and/or rate of exchange of hydrogen at a peptide amide hydrogen on at least one other endopeptidase fragment in said population of sequence-overlapping endopeptidase-generated fragments,

wherein said quantities are corrected for back-exchange losses subsequent to the initiation of slowed exchange conditions in an amino acid sequence-specific manner.

19. A method according to claim 4, wherein labeled peptide amides are localized in an amino acid sequence-specific manner by measuring rates of exchange as a function of time under slowed exchange conditions.

20. A method according to claim 4, wherein said population of sequence-overlapping endopeptidase-generated fragments contains a plurality of sequence-overlapping fragments, wherein more than half of the members of said population have sequences that overlap other members of said population over all but 1-5 amino acid residues.

21. A method according to claim 4, wherein a majority of members of said population of sequence-overlapping endopeptidase-generated fragments is present in an analytically sufficient quantity to permit its further characterization.

22. A method according to claim 4, wherein determining the quantity and rate of exchange of peptide amide hydrogen(s) is carried out contemporaneously with generating a population of sequence-overlapping endopeptidase-generated fragments.

23. A method according to claim 4, further comprising determining off-exchange rates of labeled peptide amides under conditions of slowed hydrogen exchange and random-coil conditions from a plurality of fragments and fragment differences.

24. A method according to claim 4, wherein said isotopic hydrogen is deuterium.

25. A method according to claim 24, wherein the presence and quantity of said deuterium on said fragments of said labeled protein is determined by measuring the mass of said fragments.

26. A method according to claim 4, wherein said measuring is performed using mass spectrometry.

27. A method according to claim 4, further comprising the use of conditions that effect protein denaturation under slowed exchange conditions prior to generation of said fragments.

28. A method according to claim 27, wherein said conditions comprise contacting said labeled protein with guanidine hydrochloride at a concentration of about 0.05 - 4 M.

29. A method according to claim 27, wherein said conditions comprise contacting said labeled protein first with guanidine thiocyanate at a concentration of about 1.5 - 4 M, followed by dilution into guanidine hydrochloride at a concentration of about 0.05 - 4 M.

30. A method according to claim 4, further comprising disrupting disulfide bonds in the labeled protein prior to generating said fragments.

31. A method according to claim 30, wherein said disrupting comprises contacting the labeled protein with a phosphine.

32. A method according to claim 1, wherein said experimental hydrogen exchange analysis utilizes NMR.

33. A method according to claim 1, wherein said set of predicted possible structures contains at least 100 structure predictions.

34. A method according to claim 1, wherein said set of predicted possible structures contains at least 1,000 structure predictions.

35. A method according to claim 1, wherein said set of predicted possible structures contains about 1,000 to about 10,000 structure predictions.

36. A method according to claim 1, wherein said set of predicted possible structures is predicted with the Rosetta algorithm.

37. A method according to claim 1, wherein said calculated rates of amide hydrogen exchange are determined using COREX algorithm.

38. A method of structure prediction and/or determination of a protein of interest of unknown structure, said method comprising:

comparing calculated rates of amide hydrogen exchange determined for a set of predicted possible structures for said protein of interest using thermodynamic parameters of each amino acid residue in said protein of interest defined by hydrogen exchange analysis with experimental hydrogen exchange analysis of said protein, and identifying one or more structures from said set of predicted possible structures having a calculated exchange rate profile closely matching the experimental exchange rate profile.

39. A method of performing molecular replacement, said method comprising orienting and positioning the structural coordinates for the three-dimensional structure prediction(s) for a protein obtained by the method of claim 1 within the crystallographically-obtained unit cell of the structurally unknown protein, so as best to account for the observed diffraction pattern of the structurally unknown protein crystal.

40. A method according to claim 39, wherein accurate structural predictions are identified by the degree to which said orienting and positioning of said three-dimensional structural predictions fall within the unit cell accounts for the observed diffraction pattern.

41. A method for improving the accuracy of possible predicted possible protein structure(s), said method comprising determining the degree to which predicted structures appropriately have experimentally determined fast amides on the surface thereof, and selecting predicted structures which most closely match the expected number and/or identity of fast amides on the surface thereof as more accurate models of protein structure.

42. A method according to claim 41, wherein the identity of surface-located fast amides in a protein are experimentally determined by hydrogen exchange analysis.

43. A method of performing molecular replacement, said method comprising orienting and positioning the structural coordinates for the more accurate three-dimensional structure prediction(s) for a protein obtained by the method of claim 41 within the crystallographically-obtained unit cell of the structurally unknown protein, so as best to account for the observed diffraction pattern of the structurally unknown protein crystal.

44. A method for selecting more accurate predicted protein structure(s) from among a plurality of predicted protein structure(s), said method comprising determining the degree to which predicted structures appropriately have experimentally determined fast amides on the surface thereof, and selecting predicted structures which most closely match the expected number and/or identity of fast amides on the surface thereof as accurate models of protein structure.